

# Late Complaints after Erythema Migrans

Herta Klade,\* M.D., Elisabeth Aberer, M.D.

Department of Dermatology, Division of General Dermatology (H.K.) and Division of Immunology, Allergy and Infectious Diseases (E.A.), University of Vienna, Vienna, Austria

A lot of treatment studies have been carried out, but no antibiotic has been proved to avoid late manifestations of Lyme disease. Our interest focused on late manifestations following uncomplicated erythema migrans (UEM) and complicated erythema migrans (CEM) after a median observation period of 30 months. To compare the therapeutic, serological, and clinical outcome, 161 patients were re-examined prospectively. Late complaints could be observed in 31/161 (19%) of patients, more often in UEM than in CEM (36% versus 12%). Patients with late sequelae were more often seropositive than the total collective (77% versus 67%), at least once during the observation period, as against 12 of 13 patients who needed several therapy cycles (92%). Seven seropositive patients did not respond to oral antibiotic treatment even after several cycles. Amoxicillin/clavulanic acid treated patients had late complaints in 8% in contrast to penicillin V (15%) and doxycycline (17%) treated persons. Seropositivity before treatment has a negative influence on the course of erythema migrans (EM) disease. Immunogenetic disposition might be responsible for repeated infections and for treatment failures in a certain patient group.

**Key words:** Erythema migrans, Complicated and uncomplicated, Late complaints, B. burgdorferi-antibodies

## INTRODUCTION

First reports on the relation of erythema migrans (EM) to tick bites date back to the beginning of this century (1). In the early fifties, it was reported that antibiotics efficiently act on EM (2). With the detection and characterization of a previously unknown spirochete from *Ixodes (I.) dammini* ticks by Burgdorfer et al. in 1982 (3), the door was opened to study its antimicrobial susceptibility *in vitro* and *in vivo* (4-7). Several therapeutic studies have been carried out by different groups of researchers (4, 5, 8-13) to ascertain the best antibiotic treatment in early Lyme borreliosis in order to prevent late manifestations of the disease, as well as serological studies, to investigate the role and effect of specific antibodies in EM and associated complaints (14-18). For oral treatment following intensive use of penicillin, tetracyclines were found to be superior (4). Erythromycin, highly effective *in vitro*, resulted in more treatment failures than penicillin or tetracycline (4). A well-documented report describes the effectiveness of amoxicillin combined with probenecid or doxycycline for 21 days (11), and a randomized study supports the use of ceftriaxone intramuscularly (13).

## MATERIALS AND METHODS

**Patients.** One hundred sixty-one patients (116 female, 45 male) with EM were reinvestigated after therapy in the following 6, 12, and 24 months and up to 5 years (median 30 months) a minimum of four times. Every patient's history

was evaluated with respect to arthralgia, polyarthritides, headache, fatigue, fever, and cardiac and autoimmune diseases. Patients with a history of these symptoms before the onset of EM were excluded.

Erythema migrans was classified as uncomplicated erythema migrans (UEM), when no accompanying symptoms were noted, and as complicated erythema migrans (CEM), when the occurrence of EM was accompanied by systemic symptoms (e.g., fatigue, fever, chills, headache, migratory musculoskeletal pains, and arthralgia).

Any symptoms that occurred during the observation period were recorded. These were viewed as late manifestations of the spirochetal infection when a concomitant infectious disease, trauma, or other underlying degenerative disease could be excluded.

In patients with an elevated IgG antibody level and negative IgM antibodies less than 4 weeks after the tick or insect bite or beginning of EM, a second episode of Lyme disease (re-infection) was considered (14, 19, 20).

**Treatment.** Ninety-four patients with EM received oral phenoxymethylpenicillin 1.5 million IU bid for 10 to 14 days, 35 were treated with doxycycline 100 mg bid orally for 10 to 14 days, and 12 patients received amoxicillin 500 mg plus clavulanic acid 125 mg bid orally for 20 days. Because of persistent concomitant symptoms like arthralgia, cephalgia, fatigue, polyarthritides, myalgia, fever, and lymphadenitis in CEM, or arising complaints in UEM during or up to 1 month after therapy, six UEM and seven CEM patients required retreatment. The sequence of antibiotic therapies was varied, but in all regimens, penicillin or doxycycline were primarily used, and all patients received both antibiotics. Seven patients refused antibiotic therapy (Table 1).

**Serological methods.** Antibodies against *Borrelia (B.) burgdorferi* were evaluated by enzyme-linked immunosorbent assay (ELISA) (21) before, 3 to 5 weeks after, 6 months after, and 2 to 5 years after treatment. An ELISA unit of 4.7 was calculated as the threshold level. A supernatant of an ultrasonicated whole cell preparation of *B. burgdorferi*

\*Corresponding author.

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## LATE COMPLAINTS AFTER ERYTHEMA MIGRANS

TABLE 1  
 Frequency of Late Complaints in Patients with UEM and CEM at the Last Follow-Up After a Mean Period of 3 Years

Patient	161 PATIENTS				31 PATIENTS (19.3%)			
	UEM 128 (79.5%)				CEM 33 (20.5%)			
T								
H								
E								
R								
A								
P								
Y	6	79	26	11	5	6	1	15
L	2	10	4	0	3	1	4	4
A	33.3%	12.7%	15.4%	0%	50%	100%	27%	57.1%
T								
E								
C								
O								
M								
P								
L								
A								
I								
N								
S								

UEM = uncomplicated; Pen. = phenoxymethylpenicillin; Dox. = doxycycline; Amox./Clav. = amoxicillin/clavulanic acid; More Ther. = several antibiotic cycles.  
 There was a high significant difference in the occurrence of late complaints between UEM and CEM ( $p < 0.01$ ) and a significant difference between the treatment groups in relation to late complaints in UEM ( $p = 0.046$ ) in contrast to CEM ( $p = 0.185$ ).

B31 strain, 1 µg per well, was used as an antigen. Photometrically determined optical density (OD) values were quantified in ELISA units, defined as the differential value of the base 5 logarithmic dilution at OD 0.2 from the comparison of a known positive serum with the test serum. **Statistical analyses.** The analyses were calculated by a chi-square test; values  $< 0.05$  were interpreted as significant.

## RESULTS

- 1) **Clinical course**
- The median observation period was 30 months (22 months to 5 years).
  - Tick bites were reported in 53 patients (32.9%), insect bites from mosquitoes or horseflies in 46 patients (28.5%), an undetectable spider bite in 1 patient, and a thorn injury in 1 patient. No specific data were given for 60 patients (37.5%).
  - A total of 128 patients had UEM (79.5%), and 33 patients had complicated CEM (20.5%) (Table 1).
  - Median duration of EM before treatment was 26 (3 to 270) days (UEM 21 days and CEM 38 days); median duration

TABLE 2  
 Late Complaints

	UEM (n = 119)	CEM (n = 12)
Monosymptomatic	13	3
Polysymptomatic	5	9
Monarthralgia	4	2
Oligoarthralgia	8	1
Arthritis	3	1
Dyspareunia	2	2
Cephalgia	2	4
Myalgia	2	3
Fatigue	4	2
Depression	4	1
Acrodermatitis chronica atrophicans	—	1
Neuropathy	1	—
Neuroarthral nodules	1	—
Neuralgia	2	—
Carpal tunnel syndrome	1	—

of EM with subsequent late complications was 46 days (UEM 56 days and CEM 21 days).  
 • The most frequently recurring late complaints (Table 2)

Table 3  
Late Complaints of 161 EM Patients Depending on Treatment

EM	Number of Patients		Late Complaints (%)
	(n)	(%)	
Penicillin	94	14	14.9
Doxycycline	35	6	17.1
Amoxicillin/Clavulanic acid	12	1	8.3
More therapy cycles	13	7	53.8
Untreated	7	3	42.9

were mild to moderate severe mono- and oligoarthralgias, starting between 2 and 36 months after EM and lasting from 3 to 42 months. The predominant localization was that part of the body with previous EM. Arthritis occurred only in one patient with primary CEM. Dactylitis with painful swelling of the fingers could only be observed after UEM and fatigue only after CEM. In addition, in the CEM group, one patient developed acrodermatitis chronica atrophicans (ACA) of the legs three years after EM and one circumscribed scleroderma at the site of EM after half a year.

Recurring complaints after more than 2 years were seen in 19 patients with UEM (41.18%) and in 12 patients with CEM (36.4%) (Table 1).

Treatment

Erythema migrans cleared in all patients after several days. Penicillin and doxycycline proved equally effective in preventing late complaints (85/87% in UEM, 73/78% in CEM) (Tables 1 and 3). Amoxicillin/clavulanic acid was ineffective in one patient with CEM but had no treatment failure in UEM. Patients who needed more than one therapeutic cycle did not recover in up to 53.8% of the cases. Jarisch Herxheimer-like reactions at the beginning of treatment and in 4/33 patients with CEM. Manifestations included flu-like symptoms, fever, chills, and fatigue.

Serological findings

At least once during the observation period, 108 patients (67%) were seropositive (Table 4); this includes 24 out of 31 patients seropositivity before therapy and at the time of the last control was roughly 50% (Table 6).

Doxycycline-treated patients developed antibodies to *B. burgdorferi* more often than penicillin-treated patients, but without statistical significance. After treatment with amoxicillin/clavulanic acid, the number of seropositives was lowest. Patients who received more than one therapy cycle were seropositive in a higher percentage than untreated patients (92.3% versus 71.4%).

Table 4  
ICM and/or IGC-Antibodies against *B. burgdorferi* at Least Once during Observation Period

	ICM and/or IGC-Antibodies against <i>B. burgdorferi</i> at Least Once during Observation Period	
	CEM	ALL EM
Penicillin	48/79 (60.7%)	12/15 (80.0%)
Doxycycline	28/26 (69.2%)	8/9 (88.9%)
Amoxicillin/Clavulanic acid	4/11 (36.4%)	1/1 (100%)
More therapy cycles	5/6 (83.3%)	7/7 (100%)
Untreated	4/6 (66.7%)	1/1 (100%)
Total	79/128 (71.8%)	29/33 (87.9%)

IgM antibodies were found positive in 15.6% of the cases before therapy and decreased to 11.9% after therapy (data not shown). In UEM patients, IgG seropositivity before therapy was seen in 36.7%, as against 42.5% after therapy. In contrast, in CEM patients, 72.7% were seropositive before and 62.9% after therapy.

At the last control, 62 of all patients were seropositive (38.5%); 45 of the UEM group (35.2%), and 17 of the CEM group (51.5%) (Table 5). Patients with UEM and late symptoms were more often seropositive (47/7%) than patients without late symptoms (33/0%), however, no statistical relevance could be explained. In contrast, at the last control, patients with CEM and late complaints were only seropositive in 41.7% versus 57% of patients without persistent complaints. In the doxycycline group, 50% of the patients with late symptoms were seropositive, whereas only 35.7% of the penicillin-treated patients were seropositive.

Reinfection

According to the definition, a *B. burgdorferi* reinfection was suspected in 28 of the 161 patients (17.4%) due to IgG seropositivity before treatment at a median duration of EM of 12 days; 10 of these 28 patients developed late complaints (35.7%; UEM 47.1% versus CEM 18.9%;  $p = 0.000$ ).

DISCUSSION

Erythema migrans can be diagnosed clinically except in atypical cases, but it is still difficult to identify complaints that appear weeks or months after clearing of EM by antibiotic treatment as being late manifestations of Lyme disease (22-24).

According to reports in the literature, late complications such as arthralgias, headache, and fatigue have been associated with chronic Lyme borreliosis in seropositive and seronegative patients (25). In our patients, arthralgia and dactylitis caused by swelling of the inter-articular connective tissue appeared clinically as tenderness on pressure. Joint alterations demonstrable by X-ray were never observed. Dactylitis was seen in association with UEM, whereas fatigue was only observed in patients of the CEM group (25). Migratory musculoskeletal pains either persisted from several months to more than 3 years or recurred after symptom-free intervals. Dyspareunia could be confirmed by clinical neurological examination. Headache and fatigue in our patients were of subjective nature. Because of the prospective follow-up and the personal knowledge of patients, statements of patients could be evaluated objectively. For the patients, the complaints were disturbing life quality for a certain time, but they have not been seen as severe as to cause encephalopathy or disabling "rheumatic" or cardiac

Table 5  
IGC-Seropositive Patients at the Last Control

	No Late Complaints (n = 130)		Late Complaints (n = 31)		Total
	UEM	CEM	UEM	CEM	
Penicillin	34/94 (36.2%)	22/69 (31.9%)	7/11 (63.6%)	2/4 (50.0%)	5/14 (35.7%)
Doxycycline	13/35 (37.1%)	7/12 (58.3%)	3/7 (42.9%)	0/2 (0.0%)	3/6 (50.0%)
Amoxicillin/Clavulanic acid	2/12 (16.7%)	2/11 (18.2%)	0/0 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
More therapy cycles	8/13 (61.5%)	2/3 (66.7%)	2/3 (66.7%)	2/4 (50.0%)	4/7 (57.1%)
Untreated	5/7 (71.4%)	3/4 (75.0%)	0/0 (0.0%)	1/1 (100%)	2/3 (66.7%)
Total	62/161 (38.5%)	36/109 (32.9%)	12/21 (57.1%)	5/12 (41.7%)	14/31 (45.2%)

Table 6  
Comparison of IGC-Antibodies against *B. burgdorferi* in Patients with Late Complaints before Therapy and at Their Latest Control

	Before Therapy	Latest Control
UEM	9/19 (47.4%)	9/19 (47.4%)
CEM	7/12 (58.3%)	5/12 (41.7%)
TOTAL	16/31 (51.6%)	14/31 (45.2%)

disease. All these symptoms improved gradually during the observation period, as also reported by Steere et al. (27). The importance of critical view of complaints is addressed in a recent retrospective study of 82 patients, who were treated adequately or nonadequately for cutaneous manifestations of Lyme borreliosis (28). Several systemic complaints were described in these patients. Although symptoms like arrhythmical blocks caused by hypertensive cardiomyopathy, polyneuropathy after acrodermatitis chronica atrophicans, or carpal tunnel syndrome have been associated with Lyme borreliosis, these were attributed to old age or chronic alcoholism in this study.

One of the factors influencing the course of Lyme disease has been seen in the duration of CEM, as it was twice as long in patients with CEM than in UEM. In most of the treatment studies of early Lyme disease, antibiotics were given within the first 4 weeks of illness (9, 10, 12). Asbrink and Olsson, however, reported on general symptoms in 53% in patients with a disease duration longer than 3 weeks, compared to 23% of EM lasting less than 3 weeks (12). A significant correlation between the duration of therapy and clinical outcome was not found by others (13).

The evaluation of the efficacy of the various antibiotics used in this study is restricted because of the heterogeneity of our patient groups with regard to the type of antibiotic and duration of treatment. Unresponsiveness to the first treatment schedule and ongoing systemic symptoms despite clearing of EM was observed in 8% of patients. Despite several antibiotic treatment cycles, the complaints did not improve after oral therapy in 7 of 13 cases. Persisting complaints seen in these patients were present even more often than in patients who refused therapy (Table 3). This is in accordance with reports by Steere et al. (23) and Sigal and Pfaller (24) who noticed that musculoskeletal symptoms will

not improve in a certain percentage of patients even after repeated administration of antibiotics. It was further shown that the response to several different antibiotics may be determined by genetic variations of the host immune response, especially, the presence of HLA-DR4 was significantly associated with the failure of treatment, (29) although this association could not be observed in Europe, as reported by Herzer (22).

A significant anti-*B. burgdorferi* antibody titer was always concomitant with worse prognosis, in that patients unresponsive to treatment were seropositive in 92% and that CEM patients were seropositive in a higher percentage than UEM patients. The epidemiologic range of seropositivity to *B. burgdorferi* in healthy blood donors has been evaluated as 8% for the area of Vienna where this study was also done (30). As reported onset, and IgG antibodies appear within 4 to 6 weeks to develop (14, 19, 20). We assumed that IgG antibodies detectable earlier than 4 weeks after tick or insect bite might point to previous contact with *B. burgdorferi*. The possibility of reinfection was repeatedly mentioned in the literature (31). Seropositivity before therapy, due to a long duration of EM or due to reinfection, predict a more severe course of disease by developing CEM or causing late symptoms.

The pathogenesis of late complaints must remain unanswered. In case of the detection of *B. burgdorferi* DNA in body fluids or affected tissues, persistent infection can be suggested (34). Viable borreliae can escape eradication by antibiotics due to intracellular location (35), can withdraw into immune-privileged sites or can persist in the host through antigenic variation similar to *B. hermslii* (19, 32, 33). On the other hand, nonviable remnants of borreliae such as surface blebs, borrelia antigens, or tissue components acting as antigens by molecular mimicry can maintain inflammatory processes (23, 36-38).

Considering all these possible hypotheses, further studies are needed for optimizing the choice of antibiotics and the duration of therapy.

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